It's not always infection:
A case of sulfasalazine-induced hypersensitivity syndrome

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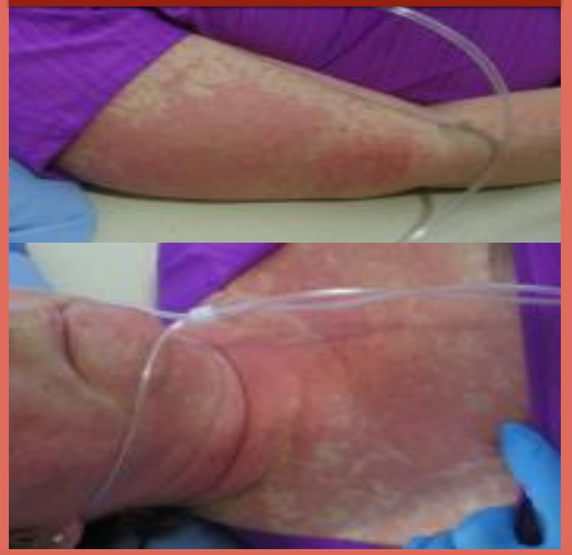
Background

- Sulfasalazine is an anti-inflammatory drug used in the treatment of various inflammatory diseases
- Common side effects include headache, nausea, fever and rash. Rarely, patients may develop complications including hepatitis, pneumonitis, haemolysis and Stevens-Johnson Syndrome
- Severe adverse reactions from this drug are typically delayed

Case

- A 52-year-old lady presented to the Emergency Department with an eight-day history of fevers and nausea
- Medical history was significant for a recent diagnosis of rheumatoid arthritis for which the patient had commenced sulfasalazine in the community with no known drug allergies
- One day prior to admission the patient had developed a new diffuse, maculopapular rash on the limbs and trunk with increasing dyspnoea
- At presentation, the patient was systemically unwell, with a tachycardia of 110 beats per minute, a respiratory rate of 28, and a fever in excess of 39 degrees Celsius
- A diffuse macular rash was noted on the trunk and all four limbs (see: *image 1*). There was no mucosal involvement, no blistering, and no desquamation.
- Empiric intravenous co-amoxiclav and oral clarithromycin was commenced, covering for a presumed lower respiratory tract infection
- Multiple sets of blood cultures were drawn, with no growth, and testing for SARS-CoV-2 by PCR was not-detected
- Blood results demonstrated a significant hepatitis, as noted in *Table 1*.
- The patient's viral and autoimmune liver screens were not significant. Liver ultrasound was normal with a patent portal venous system. CT Pulmonary Angiogram noted no pulmonary embolism but significant pneumonitis
- On re-questioning, the patient reported that the first prescription of sulfasalazine was just four weeks pre-admission. The patient had stopped the drug after only one week owing to an 'intolerance'. Sulfasalazine was restarted one day prior to the new symptom onset, resulting in fevers, rash and ultimate hospitalisation
- Sulfasalazine was held and the patient began to improve
- During admission, a deterioration occurred following the administration of furosemide for presumed new pulmonary oedema. This caused the patient's pneumonitis to progress clinically, with increasing dyspnoea together with worsening of rash and new fever
- Diuresis was stopped and the patient was started on high dose prednisolone (1mg/kg OD PO), making a full recovery
- The patient was prescribed atovaquone for the duration of therapy for Pneumocystis Jiroveci Pneumonia (PJP) prophylaxis. Trimethoprim/sulfamethoxazole was not commenced due to the risk of cross reactivity causing a subsequent reaction.

Image 1 – Diffuse macular rash seen on patients limbs and trunk *(patient consent obtained for use of image)*



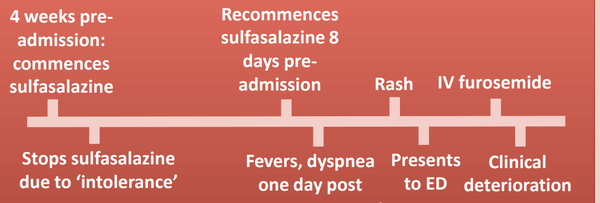


Table 1: Initial Laboratory Results

AST	704 U/L	**WCC**	6.7 10^9/L	**Urea**	7 mmol/L
Alt	903 U/L	**N/L**	5.33 10^9/L	**sCR**	123 mmol/L
Bili	16 U/L	**Eos**	0.18 10^9/L	**Na**	139 mmol/L
ALP	381 U/L	**plts**	232 10^9/L	**K**	4.2 mmol/L
GGT	341 U/L	**Hb**	15.2 g/dL	**CRP**	130 mg/L
Albu	46 g/L	**PT**	13.7 sec	**D-dimer**	6000 ng/mL

Discussion

- This case is remarkable for its demonstration of a severe drug induced hepatitis and pneumonitis with fever, identifiable only through a thorough patient history and awareness of the non-infectious aetiologies of fever
- It highlights the well-documented temporality of re-exposure to sulfasalazine inducing a hypersensitivity reaction[1]. Onset of injury is more rapid with rechallenge and can appear within a day of re-exposure
- Notably, receipt of furosemide, another non-antimicrobial sulfonamide, resulted in a further clinical deterioration while in hospital
- Antimicrobial and non-antimicrobial sulfonamides have a different chemical structure. Sulfonamide antibiotics uniquely contain an arylamine (NH2) side chain at the N4 position, a 5- or 6-member aromatic heterocyclic ring and one or more nitrogen groups at the N1-sulfonamide position. Theoretically, therefore, the two drugs should not cross-react
- However, it has been suggested that patients who have a hypersensitivity reaction after receipt of a sulfonamide antibiotic are more likely to have a subsequent reaction to non-sulfonamide antibiotics [2]. This appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs, as they also showed an association between sulfa-allergies and penicillin allergies.
- Future avoidance of sulfonamides has been advised to this patient, though the cross-reactivity of antimicrobial and non-antimicrobial sulfonamides remains debated.[2,3]

References

1. J W, L L, SM B, M M. Case of relapsing sulfasalazine-induced hypersensitivity syndrome upon re-exposure. *BMJ Case Rep*. 2020;13(9). doi:10.1136/BCR-2020-235803
2. BL S, R S, AJ A, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med*. 2003;349(17). doi:10.1056/NEJMOA022963A
3. Z, P L, A B, WJ P. Cross-reactivity in drug hypersensitivity reactions to sulfasalazine and sulfamethoxazole. *Int Arch Allergy Immunol*. 2010;153(2). doi:10.1159/000312632